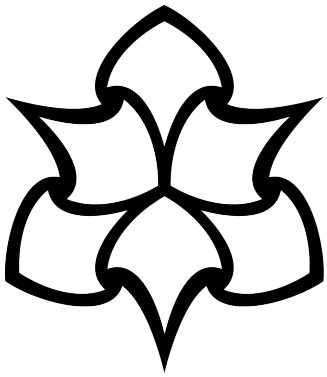

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Antimicrobial strategies to reduce polymer biomaterial infections and their economic implications and considerations

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ABSTRACT

Healthcare acquired infections (HAI's) are a worldwide problem that can be exacerbated by surgery and the implantation of polymeric medical devices. The use of polymer based medical devices which incorporate antimicrobial strategies are now becoming an increasingly routine way of trying to prevent the potential for reduce chronic infection and device failure. There are a wide range of potential antimicrobial agents currently being incorporated into such polymers. However, it is difficult to determine which antimicrobial agent provides the greatest infection control. The economics of replacing current methods with impregnated polymer materials further complicates matters. It has been suggested that the use of a holistic system wide approach should to be developed around the implantation of medical devices which minimises the potential risk of infection. However, the use of such different approaches is still being developed. The control of such infections is important for individual patient health and the economic implications for healthcare services.

1. Introduction

The association between microbial contamination and its role in the potential to lead to pathogenic infection is well established (Ashbolt, 2004; Weber and Rutala, 2013; Kenters et al., 2015; Marra et al., 2017). Healthcare acquired infections (HAI's) have become a major problem with 2011 UK data suggesting that an overall 6.5% of NHS patients have contracted a HAI. In the USA, the Centers for Disease Control (CDC) reported a 4% likelihood of a patient contracting a HAI throughout the duration of their hospital care (Centers for Disease Control and Prevention, 2016).

Whilst almost all pathogens have the potential to become problematic in hospitalised patients, the aetiology of most HAI's can be traced back to a few bacterial species namely *Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli,* coagulase-negative staphylococci (CoNS) (predominantly *S. epidermidis*) and *Enterococcus* spp. (predominately *E. faecalis* and *E. faecium)* (Martin et al., 1989; Emori and Gaynes, 1993; Bereket et al., 2012). For indwelling devices, it is often the location of the implant that dictates the most likely colonising pathogen. For instance, vascular implants are more likely to experience colonisation by coagulase-negative staphylococci and *S. aureus*, while *E. coli* and Enterococcus sp. were most likely to be recovered from urinary devices (Zhang et al., 2017). Potentially, this could make the task of controlling nosocomial infections sound relatively straightforward. However, the complexity of the bacterial cell and surface interface and the ever increasing prevalence of antimicrobial resistant pathogens (AMR) makes controlling such scenarios complicated and has led to global concerns (Jones, 2001; Andersson and Hughes, 2010; Laxminarayan et al., 2013).

Today, microbial resistance to nearly every current antibiotic has been observed (Jones, 2001). This was highlighted by the reporting of over 2 million AMR infections in the USA in 2013 alone. It has been estimated that in the last 20 years, 6%–14% of all hospitalised patients have developed a nosocomial infection associated with either an internal or partially internal medical device (Malheiro and Simões, 2017).

2. Uses, properties and types of indwelling polymeric medical implants

The use of synthetic polymers in a medical capacity began with the introduction of polypropylene (PP), nylon, and polyester sutures in World War II (Gilbert, 1999; Dumitriu, 2001). Since this beginning, many common and vital procedures now rely on the use of polymers, including, catheters (epidural, urinary and vascular), cardiovascular devices (pacemakers, heart valves and left ventricular devices) and stents (vascular and urinary). Additionally, the subsequent decades have also seen many more polymers find application within the clinical setting, however, a few still account for the majority of uses. These

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include polyvinyl chloride (PVC), polyolefins (polyethylene (PE), polypropylene (PP)), polystyrene (PS), polyurethane (PU) and silicon (Lambert et al., 2001; Gunatillake and Adhikari, 2016).

The use of a range of polymers has continued to grow within the medical field due to the materials diverse malleability, chemical properties, robust functionality, simplicity of production and low cost of raw materials (Lambert et al., 2001; Maitz, 2015). In addition, for indwelling devices, more advanced mechanical properties can also be exploited. For example, there has been the development of 'smart' polymers that can react to the use of pH, temperature, magnetic field or light for use in specific applications (Aguilar and Roman, 2014; Weems et al., 2017).

3. Biological mechanisms of device failure and the development of infection risk

Microbial contamination is often cited as a common reason for the failure of indwelling medical device due to biofilm formation, encrustation and blockage (Veerachamy et al., 2014). A biofilm can be described as a consortium of irreversibly surface associated independent cells with an extraordinary degree of organisation, embedded in a predominantly extracellular polysaccharide and water (80–90%) matrix (Donlan, 2002; Azevedo et al., 2017b; Stoica et al., 2017).

3.1. Biofilm formation

The major concern with microbial colonisation on biomaterial surfaces is the development of biofilms which due to their recalcitrant nature, can cause serious infection and device malfunction and removal (Mermel et al., 2009). Biofilms are now known to be responsible for 65% of nosocomial infections (Malheiro and Simões, 2017). The process of microbial colonisation and biofilm formation starts by the conditioning of the surface. In the case of indwelling devices this process occurs almost instantaneously after implantation. For venous implants, this process is facilitated by the deposition of organic macromolecules which form a conditioning film such as pyruvate, glucose and fibrinogen. For urinary implants, the conditioning film is compiled of proteins (e.g. Tamm-Horsfall protein), electrolytes (e.g. magnesium and calcium ions), and other organic molecules (Murga et al., 2001; Trautner and Darouiche, 2004; Nicolle, 2014). Following the attachment of a conditioning film (Fig. 1), the attachment of phenotypic pioneer species facilitates surface colonisation of bacteria and development of the biofilm (Fig. 1). These microcolonies allow for the attachment of further species which can result in a multi-layered, multispecies biofilm. The complex architecture displayed by biofilms allows for the coexistence of a vastly different, but cohesive multicellular ecosystem with cooperative and antagonistic interactions, which may include a variety of pathogenic microbes (Flemming et al., 2016a; Bowen et al., 2017). However, it is interesting to note that in some scenarios, for example hip replacements, infection is often only due to single bacterial species (Tunney et al., 1998).

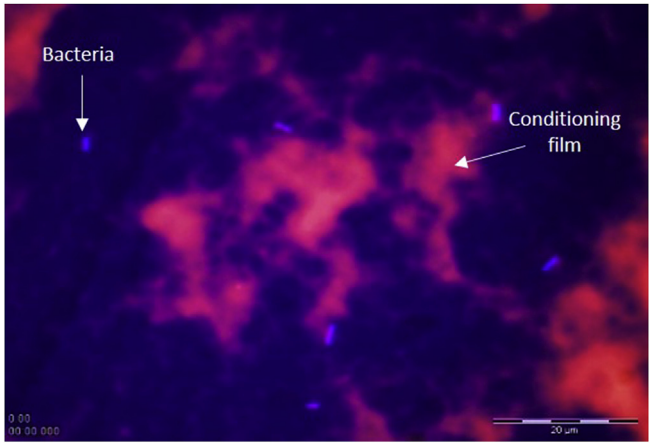

Fig. 1. Double epifluorescent staining (DAPI and Rhodamine) of cells (blue) and horse blood (red) demonstrating organic material and bacteria retained on a polymer surface following cleaning. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3.2. Biofilm dispersal

Biofilm dispersal is the final stage of biofilm development and results in the colonisation of new locations, posing a significant threat to the host. Dispersal is a highly regulated process during which some microbes undergo a phenotypic transition from a relatively slow growing collective, to an often highly motile individual and/or multicellular aggregate (Petrova and Sauer, 2016). The inter- or intra-species release of quorum-sensing (QS) molecules, such as acylhomoserine lactones, diffusible fatty acids and peptides, can influence the dispersal rate (Petrova and Sauer, 2016). Interspecies QS has also been reported, with many organisms being able to act or initiate specific behaviour in other microbial species. This can be especially significant in clinically important pathogens and the onset of co-infections (Silvester et al., 2017). More recently, the discovery that biofilms can communicate using long range electrical signals has raised questions about how novel, potential mechanisms in biofilms cause infection and enhance the development of AMR (Humphries et al., 2017; Liu et al., 2017).

3.3. Biofilm antimicrobial resistance mechanisms

Biofilms can often be found to be up to a thousand times more recalcitrant towards antimicrobials. These high levels of resistance can be acquired by utilising a wide variety of mechanisms, and often multiple mechanisms are employed in conjunction (Fig. 2). The architecture of the biofilm is not uniform (Fig. 3) and will be dependent on the microbial species involved and environmental conditions (Whitehead and Verran, 2015).

3.4. Extracellular polymeric substance (EPS)

Exopolymeric substances (EPS) are composed of glycoproteins and polysaccharides and their structure provides a mechanism for survival in host conditions, as well as a means to avoid the host immune response (Fig. 4). In addition, EPS secreted by biofilms produces electrostatic forces that can provide the structural integrity for biofilm aggregation and which can also enable surface adhesion (Flemming et al., 2016a,b). Whilst for many years the physical barrier to diffusion offered by EPS was proposed as the major resistance mechanism (Dufour et al., 2010; Singh et al., 2016) other research has suggested this may only play a minimal role in some instances (Stone et al., 2002; Stewart et al., 2009; Daddi Oubekka et al., 2012; Hall and Mah, 2017). However, antimicrobial degrading/modifying enzymes and eDNA immobilised within the polysaccharide matrix may provide a chemical barrier to the diffusion of antimicrobials and thus drug susceptibility (Dufour et al., 2010; Murakami et al., 2017).

3.5. Efflux pumps

Efflux pumps are found across all bacterial species and act as a major method of antimicrobial resistance. They are defined as a mechanism of recognition and expulsion of toxic compounds from within the cell to an external substrate before they reach their targets (McKay and Nguyen, 2017). The upregulation of efflux systems can often be in unison with other resistance mechanisms for example porin downregulation, which may be directly correlated to adverse environmental

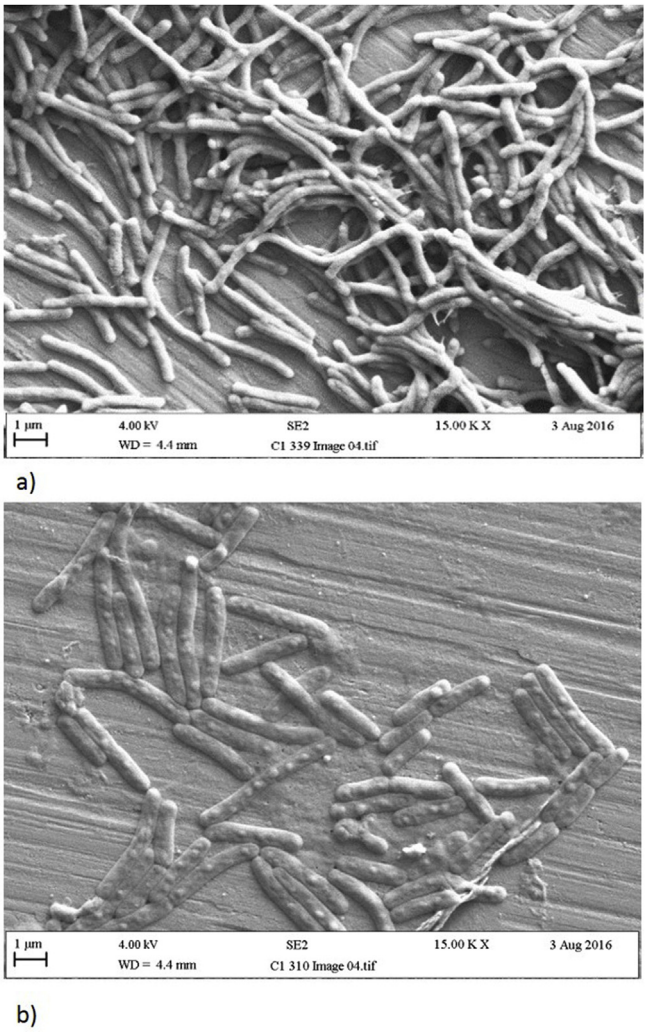

Fig. 2. SEM images demonstrating the different morphologies of bacterial cells following different chemical treatments under conditions of flow.

conditions (Martins et al., 2014). There are seven families of efflux pump which are grouped by multiple factors including the energy source (ATP hydrolysis or ion electrochemical gradient), protein sequence homology and overall protein structure. Most of these efflux systems are multidrug resistant (MDR) pumps and can transport a wide variety of structurally dissimilar antimicrobials out of the cell, however, substrate specific systems also exist (Chitsaz and Brown, 2017).

3.6. Persister cells

Persister cells are a phenotypic variant of the wild type cell whose sole function is survival in hostile conditions so that they can repopulate the biofilm (Carvalho et al., 2018). This is achieved by a distinct change in phenotypic state, to one of dormancy (Chihara et al., 2015). Dormancy reduces the impact of stressors that act on metabolically active cells (e.g. antibiotics) and can lead to a high level of multidrug resistance and as a result, recalcitrant chronic infections (Wood, 2016). The surviving population of persister cells act as a reservoir of infection, which can repopulate pathogenic biofilms after antimicrobial treatments (Del Pozo, 2018).

3.7. Heterogenicity of polymicrobial biofilms

The role of the polymicrobial biofilms in the development and outcome of infections, is still relatively unexplained. However, biofilms

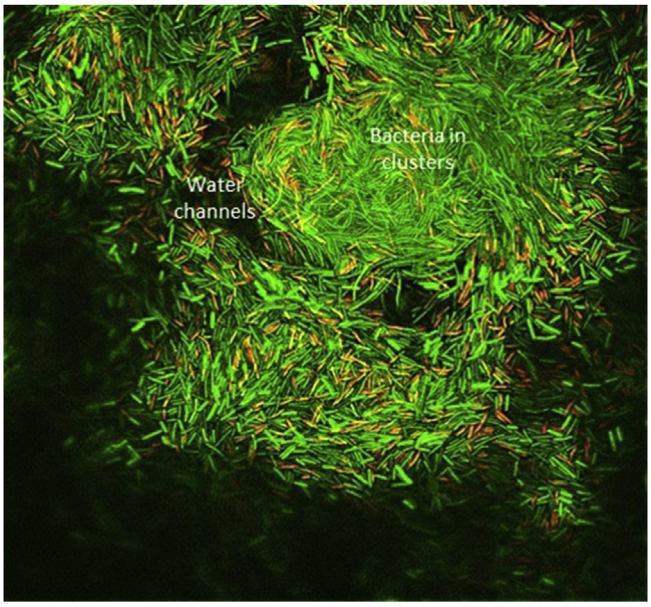

Fig. 3. Heterogeneity and viability (live cells green, dead cells, red) of a bacterial biofilm formed under conditions of flow. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

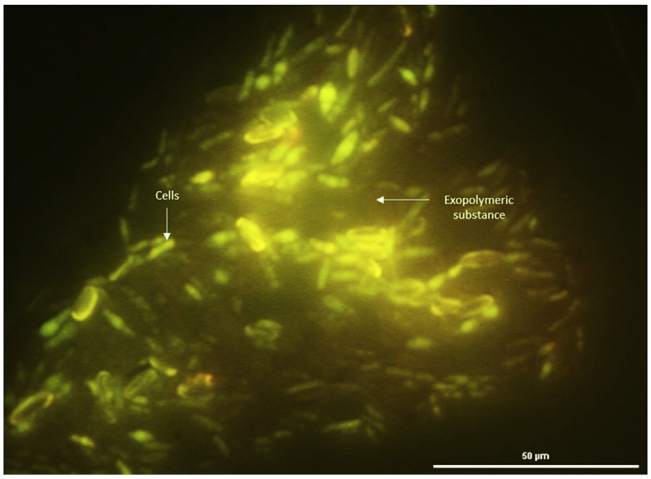

Fig. 4. Biofilm of monoculture cells demonstrating the exopolymeric substance providing a protective layer.

containing multiple co-habiting strains and species could significantly alter the optimal treatment options (Peters et al., 2012). Yurtsev et al. (2016) used a model system of two strains of *E. coli*, each producing a different antibiotic deactivating enzyme, to demonstrate that a co-culture of the two provided a significant level of cross-protection to each organism than was seen in isolated cultures. This adds to growing evidence to show that polymicrobial biofilms can provide increased interspecies antimicrobial resistance and virulence (Schlecht et al., 2015; Zago et al., 2015; Kong et al., 2016). Currently, little is known about interspecies interactions and their possible effects on biofilm formation, infection outcome and antimicrobial resistance (Azevedo et al., 2017a).

4. Current antimicrobial approaches

4.1. Incorporated chemicals

Many strategies, and especially those initially employed for

reducing microbial adhesion on indwelling medical devices have concentrated on the modification of traditional antimicrobial surface technologies. They focused largely on the incorporation of antimicrobials into a surface coating covering the implant. At the forefront of this work was the incorporation of antiseptics/biocides into the polymer matrix of the surface coating to achieve a consistent surface concentration of active agent (Russell and McDonnell, 2000). These antimicrobial systems acted by inhibiting biofilm formation through the prevention of planktonic cell adherence to the implant surface. Unlike indwelling antimicrobial systems based on antibiotic coatings, many biocidal systems have a much simpler technical formulation process and offer less chance of antibiotic resistance development (Bach, 1995). This ability is in contrast to antibiotics which have more discriminant target sites, so as to only inhibit the prokaryotic cellular processes and not interfere with eukaryotic host cells (Poehlsgaard and Douthwaite, 2005). These reasons amongst others, led to a Hygienist Panel Meeting (2010) recommending an increase in the use of medical antiseptics to fight infection and especially to provide incorporated antimicrobial protection (Leaper et al., 2010).

4.1.1. Silver

Originally, the design of antimicrobial implants emphasised catheters and coatings incorporating silver as the active microbial agent, often coupled with an organic antiseptic (Schaeffer et al., 1988; Johnson et al., 1990; Liedberg and Lundeberg 1990; Heard et al., 1998; Schierholz, 1998; Bologna et al., 1999). Schaeffer et al. (1988) used a system of silver oxide coated catheters and trichloroisocyanuric acid within a drainage bag. The results suggested that patients who received the silver incorporated catheters had a reduced rate of associated bacteriuria. The authors also suggested that antimicrobial containing catheters offered an effective way to reduce catheter-associated bacteriuria (Schaeffer et al., 1988). Likewise, Liedburg and Lundeburg (1990) examined a Foley catheter coated with a silver alloy and suggested that patients who received the silver incorporated catheter were less likely than patients who received a teflonised latex catheter to acquire a urinary tract infection. Heard et al. (1998) examined the efficacy of central venous catheters coated with a combination of chlorhexidine and silver sulfadiazine. The results showed a 12% reduction in viable surface bacteria, but this offered no reduction in the incidence of catheter related bacteraemia. Further, to this, numerous meta-analyses of results over the last two decades have suggested first generation chlorhexidine-silver sulfadiazine (C-SS) coatings on indwelling catheters offered a reduced rate of bacteraemia, bacteriuria and infection occurrence (Casey et al., 2008a; Hockenhull et al., 2008; Ramritu et al., 2008). There have been numerous studies on the antimicrobial action of silver (Table 1), and the possibilities of silver used in synergistic antimicrobial combinations with other materials for example graphene oxide and carbon nanotubes (Si and Quan, 2017; Whitehead et al., 2017). It may be possible that such antimicrobial combinations could be incorporated into catheters for use as biocidal agents.

However, a selection of similar analyses have suggested that catheters incorporating C-SS coatings had no significant effectiveness in reducing infection. Logghe et al. (1997) found this to be the case for C-SS coated central venous catheters, suggesting the antimicrobial incorporation had no effect on the rate of bacteraemia or infection. However, more positive opinions of C-SS catheters seem to have prevailed since a systematic review by Lai et al. (2016) strongly supported the C-SS coatings ability to reduce catheter-related blood infections. The authors of the latter also showed that the clinical setting and patient's condition played a large part in the overall effectiveness of the implant. This may offer some insight as to why the numerous studies have found conflicting results.

Other metallic compounds have also been incorporated into polymeric biomaterials to provide antimicrobial properties. However, for use within indwelling medical devices there is a strong bias towards silver compounds. This may be due to the conception that silver offered the highest antimicrobial efficacy of all the metals (Silvestry-Rodriguez et al., 2007). However, there is concern regarding the use of metals as antimicrobials due to their potential toxicity (Hodgkinson and Petris, 2012). It has also been suggested that combinations of metals may result in synergistic effects (Vaidya et al., 2018). McLean et al. (1993) demonstrated that a combined silver-copper coating of catheter material (butyl rubber silicon rubber, polyvinylchloride, and Teflon) produced a greater efficacy against *P. aeruginosa* than a control material or one with only silver coated surfaces.

4.1.2. Nanoparticle silver

The development of polymers containing micro-dispersed nanoparticles has provided a new method of providing a microbiocidal concentration of silver across the material surface, whilst controlling the amounts of leaching so that they remain below human cytotoxic concentrations (Guggenbichler et al., 1999). Stevens et al. (2009) incorporated silver nanoparticles into silicone catheter material and showed an increased antimicrobial activity and reduced thrombogenicity to near zero. Stevens et al. (2011) again showed that a catheter coating containing silver nanoparticles and sodium heparin could significantly reduce the adhesion of multiple *S. aureus* strains and reduce thrombogenicity to virtually zero. A clinical trial by Fichtner et al. (2010) also supported silver nanoparticle impregnation of external ventricular drainage catheters as they concluded it may reduce the risk of catheter-related infections in neurosurgical patients.

4.2. Incorporated organic compounds

4.2.1. Chlorhexidine

Although most often used as a topical treatment due to possible toxicity concerns, the use of organic antiseptics incorporated into indwelling implant is increasingly becoming common (Eltorai et al., 2016). Chlorhexidine is commonly used in combination with chloroxylenol and especially in combination with silver sulfadiazine. Chlorhexidine is a bisbiguanide and possesses broad-spectrum bactericidal and fungicidal properties (Russell and Path, 1986; Hiom et al., 1992). However, its activity is pH dependent and is reduced in the presence of organic matter such as serum. Although the mode of action is not completely defined, it is considered that initial cell membrane damage is induced by the cationic chlorhexidine interactions with the anionic phosphate groups in the bacterial lipid layer, allowing passive diffusion for the biocide to attack the cytoplasmic membrane (Table 1). This results in the leakage of low molecular weight cellular components and ultimately cell death (Sofiyanti et al., 2015).

The efficacy of chlorhexidine as a topical antiseptic is well documented, but as early as 1982 Lamb and Martin had incorporated chlorhexidine acetate in to an acrylic prosthesis for the use in the reduction of oral *Candia albicans* infections (Loe and Rindom Schiott, 1970; Hennessey, 1973; Lamb and Martin, 1983; Stalder et al., 1992; Chlebicki and Safdar, 2007; Nuntnarumit and Sangsuksawang, 2013). Although chlorhexidine and its derivatives have been used as antimicrobials, there have been studies that suggest that microorganisms show both resistance and no resistance to these products (Diehl and Chapman, 1999; Lear et al., 2006; Riazi and Matthews, 2011). In addition, chlorhexidine was incorporated into numerous catheter types in combination with silver sulfadiazine so as to provide a broad-spectrum antimicrobial action. Subsequently, chlorhexidine was also used as the single active incorporated into anti-infection polyurethane dressings for vascular and epidural catheters (Shapiro et al., 1990; Hanazaki et al., 1999; Garland et al., 2001; Mann et al., 2001; Levy et al., 2005). Ho and Litton (2006) conducted a meta-analysis of relevant clinical studies using a chlorhexidine impregnated dressing. The authors concluded that they provided an effective reduction in bacterial colonisation and were also associated with a reduction in catheter-related bloodstream infections. More recently, Kerwat et al. (2015) confirmed this finding, reporting significantly reduced bacterial colonisation to catheter tip

Table 1
Biochemical processes and mechanisms of chemical strategies.

Chemical	Biochemical process/mechanism	Reference
Silver	Generation of Reactive Oxygen Species (ROS). ROS, in-turn, cause direct damage to mitochondrial membrane and hyperoxidation of lipids, proteins and DNA.	Park et al., 2009. Kim et al., 2011. Huang et al., 2010
Chlorhexidine	Interaction with membrane cardiolipin and phosphatidylethanolamine, disturbing normal arrangement/integrity of the bilayer structure Coagulation of cytoplasmic proteins.	Cheung et al., 2012 Hugo and Longworth, 1966; Sheppard et al., 1997.
Povidine-iodine (PVP—I)	The antimicrobial activity of PVP is enhanced by the iodine that causes oxidation of reactive moieties on cell surfaces and disruption of electron transport.	Kanagalingam et al., 2015
Polyvinylpyrrolidone	Poly(vinyl pyrrolidone) (PVP), has a limitation of the lack of a reactive group. However, molecular analysis (qPCR) has confirmed that it does affect the expression of genes involved in oxidative stress and in nanoparticle form it possess positive charges that can target the negative phospholipid surface, directly increasing membrane permeability leading to disturbance of cell osmotic balance and disruption of membrane.	Krezovic et al., 2017; Milosavljevic et al., 2017; Ng et al., 2013
Benzalkonium Chloride (BAC)	A quaternary ammonium cation-based disinfectant. Binds to, and disrupts cell membranes thereby initiating autolysis and the leakage of intracellular constituents.	Ioannou et al., 2007
Triclosan	Inhibitition of bacterial fatty acid synthesis by targeting enoyl-[acyl-carrier protein] reductase	Heath et al., 1999; Levy et al., 1999
Octenidine	Interaction with membrane cardiolipin, disturbing normal arrangement/integrity of the bilayer structure. Interferes with the enzymatic systems, disturbs cell functions and leads to the leakage of the plasma membrane.	Hübner et al., 2010 Malhotra et al., 2016
Minocycline	Binding to 30S ribosomal subunit, preventing attachment of the aminoacyl tRNA to the RNA-ribosome complex	Chukwudi, 2016
Rifampin	Inhibition of DNA synthesis by targeting bacterial RNA polymerase (RNAP)	Hartmann et al., 1967
Gentamicin	Binds to h44 of 16S rRNA and binds to H69 of 70s rRNA. Inhibition of ribosomal translocation.	Moazed and Noller, 1987; Borovinskaya et al., 2007; Cabañas et al., 1978
Heparin	Reduces bacterial adhesion by inducing increased surface hydrophilicity, causing a highly hydrated interface.	Ruggieri et al., 1987
Poly(ethylene glycol) (PEG)	Reduces bacterial adhesion due to increased surface hydrophilicity.	Kingshott et al. 2003
Antimicrobial Peptides (AMPs)	Cationic molecules - allows their interaction with negatively charged components present in the bacterial membrane and cell wall. AMPs are also amphipathic allowing partition into bacterial cell membranes. Evidence of macromolecular synthesis inhibition, nucleic acid and protein synthesis inhibition, and disruption of cell wall synthesis.	Mohammad et al., 2015; Papagianni, 2003; Lehrer et al., 1989; Park et al., 1998a,b
Chitosan [poly-(*b*-1/4)-2-amino-2-deoxy-D-glucopyranose]	Binds to teichoic acids within the bacterial cell wall thereby disrupting cell shape determination and regulation of cell division, ultimately resulting in microbial death.	Raafat et al., 2008
Lactobacillus Derived Biosurfactants	Reduce surface tension and interfacial tension, inhibiting the adherence of pathogens to the surface. Also reduce the adherence capacity of several pathogens themselves thereby inhibiting biofilm proliferation and formation. Competitive exclusion has also been demonstrated.	Satpute et al., 2016; Rodrigues et al., 2006; Walencka et al., 2008; Schachtsiek et al., 2004

and insertion sites of 18% and 33% respectively, when compared with a control. However, the authors also noted that no reductions in rates of local infection were observed (Kerwat et al., 2015). A more recent meta-analysis by Safdar et al. (2014) seemed to confirm the findings of Ho and Litton since it was found that chlorhexidine-impregnated dressings significantly reduced the rates of CVC colonisation and catheter related bloodstream infection.

4.2.2. Povidine-iodine (PVP—I)

Povidine-iodine (PVP—I) is a commonly used topical antiseptic in the healthcare environment (Burks, 1998). As far back as 1985, Mandy showed treatment with a povidone-iodine-impregnated polyethylene oxide gel (PVPI-POG) dressing reduced the infection of surgical wounds when compared with a control (Mandy, 1985). Subsequently, work by others validated the antimicrobial efficacy and anti-inflammatory properties offered by iodine-containing medical sutures (Singhal et al., 1991; Polous et al., 1993). However, little further research has been published. This might be due to success of chlorhexidine (and silver compounds) as when PVP-I was compared with chlorhexidine gluconate it did not seem to be provide the same reduction in bloodstream infection when used to disinfect the catheterisation site (Chaiyakunapruk et al., 2002). The authors further suggested that this might be due to the interference of organic matter in the biocidal efficacy of PVP-I coupled with the minimal residual microbial efficacy offered by PVP-I.

4.2.3. Polyvinylpyrrolidone

Kristinsson et al. (1991) showed a reduction of microbial adherence and growth on iodine-complexed polyvinylpyrrolidone for up to 5 days. Polyvinylpyrrolidone coated catheters were commercialised under the name 'Hydrocath'. Jansen et al. (1992) investigated commercially available Hydrocath catheters complexed in polyvinylpyrrolidone and showed inhibition of *S. epidermis* adherence for up to 48 h even against proliferating bacteria in a brain heart infusion media (BHI). Romano et al. (1993) demonstrated using a mouse model, that sections of Hydrocath catheters without a teicoplanin coating developed a relatively high level of colonisation by *S. aureus* or *S. epidermidis*. In addition, it was suggested that the sections of Hydrocath without teicoplanin coatings developed surrounding abscesses. The modern Argon Hydrocath Assure™ (Argon Critical Care Systems Singapore Pte. Ltd., Singapore) range of catheters utilise both a hydrophilic polyvinylpyrrolidone coating and antimicrobial Benzalkonium Chloride (BZC) impregnation.

4.2.4. Benzalkonium chloride (BAC)

An early study by Tebbs and Elliott (1993) described the ability of a BAC impregnated catheter to reduce the *in vitro* microbial adhesion of *Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae* and *Candida albicans* and 4 strains of *S. epidermidis* in a complex human blood and PBS media. Subsequently, Moss et al. (2000) examined the implantation of a polyurethane triple-lumen central venous catheter coated with benzalkonium chloride in 117 patients, compared to a control in 118 patients. After 12 days the catheters were removed and the results suggested that the catheters coated in BAC significantly reduced microbial

contamination, when compared with the control (Moss et al., 2000). Conversely, Jaeger et al. (2001) found that BZC impregnated catheters showed no significant decrease in the incidence of microbial catheter colonisation or bacteraemia in patients with a high risk of infectious complications, when compared with a control. Further, the case presented by Shih et al. (2010) reported the suggested occurrence of anaphylactic shock induced by the implantation and allergy to a BAC coated catheter, although this was a seemingly rare case.

4.2.5. Triclosan

Triclosan is a common topical antiseptic and disinfectant used within the healthcare environment (Regös et al., 1979; Levy, 2000). The commercial incorporation of triclosan into medical products was also established with the development of Vicryl Plus® sutures (Barbolt, 2002; Storch et al., 2004; Ford et al., 2005; Edmiston et al., 2006). In 2013, Wang et al. conducted a meta-analysis on the ability of triclosan coated polyurethane sutures to decrease the development of surgical site infections. The authors examined 3720 cases and their final conclusion was that triclosan coated sutures reduced the surgical site infection rate by 30% (Wang et al., 2013). In addition, Hernández-Richter et al. (2000) used animal models to confirm triclosan incorporated dacron grafts significantly reduced the incidence of prosthesis infection when compared with a control. Hernández-Richter et al. (2003) also demonstrated triclosan incorporated vascular grafts offered an antimicrobial effect against *S. aureus* when subcutaneously implanted into an animal model. More recently, Ricco et al. (2012) revealed a preliminary experiment indicating a silver-triclosan incorporating vascular graft could provide fast acting bactericidal efficacy against MRSA. In recent years the use of triclosan has been subjected to increased regulatory scrutiny due to its increasingly ubiquitous use, suspected lack of efficacy and negative effects through environmental and anthropological accumulation. It has been recorded to have both cytotoxic and endocrine disruptive properties, as well as a propensity to photodegrade into dioxins (Aranami and Readman, 2007; Henry and Fair, 2013). It has been hypothesised that triclosan could also be a carcinogen, cause gut and oral microbiome disruption whilst also potentially being neurotoxic (Dinwiddie et al., 2014; Halden, 2016; Siddique et al., 2016; Ruszkiewicz et al., 2017). In Europe, this led to the Scientific Committee on Consumer Safety removing triclosan from the positive list of additives and its use in food contact materials became prohibited (SCCP (Scientific Committee on Consumer Products) 2011). As it is also not registered in the framework of the European regulation on biocides, it is also prohibited from use as a disinfectant in the production of food or feed. Most recently, in 2017, the FDA ruled that 23 antibacterial actives, including triclosan, could no longer be recognized as safe and effective for use in over-the-counter (OTC) health care antiseptic products. This included health care personnel hand washes and rubs, surgical hand scrubs and rubs, and patient antiseptic skin preparations since it was decided that no additional safety or effectiveness data had been provided to the FDA (FDA, 2017). Additionally, it should also be noted that that the change of public opinion, regarding the safety of triclosan, has led to the decline of manufacturers supporting its inclusion in some of their products.

4.2.6. Octenidine

Octenidine is another potential high impact antimicrobial surface coating suggested for use by a 2009 Hygienist Panel meeting to help alleviate the pressure on antibiotic use (Leaper et al., 2010). Octenidine is thought to act as a cationic surface-active compound, binding to the anionic groups in the cell membrane causing cell immobilisation and subsequent bursting (Hübner et al., 2010). Hübner et al. (2010) and Leaper et al. (2010) both supported the potential of octendine to become an incorporated antimicrobial defence which would help to replace a other additives such as chlorhexidine, PVP-I and triclosan.

So far, the development of octenidine incorporated medical products is still in development. However, Kälicke et al. (2006) showed a biodegradable poly-L-lactide (PLLA) coating incorporating both octenidine and triclosan for use on implants could potentially reduce infection rates by 66% *in vivo*. This was comparable to a similar antibiotic coating the authors tested, and led them to the conclusion that such antiseptic coatings could offer the same level of infection protection as antibiotic based coatings without the potential for development of resistance (Kälicke et al., 2006). Matl et al. (2009) showed that sutures incorporating polyglycolic acid (PGA), a biodegradable thermopolymer polymer, and octenidine showed sustained anti-infection properties, However, it has been suggested that further investigation to improve the biocompatibility of such new antimicrobial surfaces needs to be conducted (Matl et al., 2009). The inclusion of octenidine to polymethylmethacrylate (PMMA), has shown a strong antibacterial efficacy against both *S. aureus* and *P. aeruginosa* (Weckbach et al., 2012). A polymeric dental resin containing octenidine has further been shown to significantly reduced biofilm formation after 3 days and 7 days *in situ* (Rupf et al., 2012).

4.3. Antibiotic coatings

The most popular polymers for antibiotic incorporation are PMMA, poly(lactic-*co*-glycolic acid) (PLGA), poly(lactic acid), polyethylene glycol, and poly(D,L)lactide (PDLLA) (Luo et al., 2006). The impregnation, incorporation or coating of many different antibiotics has been examined with varying success however, factors can influence the efficacy including biocompatibility, retention of antibiotic activity through the formulation process (non thermolabile etc.) and the specific infectious organisms targeted. For example, the formulation and physicochemical compatibility between the antibiotics and the polymers has been shown to drastically alter the length and rate of antibiotic release (Schierholz et al., 1997). For antibiotic impregnated devices, the antibiotic is usually incorporated into the bulk material of the device just prior to injection moulding or extrusion.

4.3.1. Minocycline-rifampin

A frequently incorporated antibacterial combination into polymers is minocycline-rifampin (M-R). Raad et al. (1997) compared the use of M-R and C-SS polyurethane catheters with the results appearing to suggest that M-R incorporation had enhanced antimicrobial efficacies. For example, when incubated into serum, the antimicrobial half-life of M-R incorporated catheters was 25 days, compared to 3 days demonstrated by C-SS incorporated catheters and in rabbit models M-R coated catheters showed a significantly greater efficacy in preventing colonisation and infection with *S. aureus*. Furthermore, M-R coated catheters showed broad-spectrum efficacy which was significantly greater than C-SS coated catheters when challenged with many different strains of Gram-positive and Gram-negative bacteria or *C. albicans*. *In vivo* experiments also revealed that M-R coated catheters were highly efficacious in preventing both microbial colonisation and infection (Raad et al., 1996). Similarly, Hampl et al. (1995) examined the use of rifampin-loaded silicone catheters to reduce the potential infection of cerebrospinal fluid (CSF) shunts. These catheters provided a bactericidal concentration of rifampin for up to 60 days. Using a rabbit model inoculated with *S. epidermis* and *S. aureus* rifampin-loaded catheters to significantly reduced the incidence of CSF shunt infection from the main causative organisms (Hampl et al., 1995).

Raad et al. (1997) conducted a randomised, double-blind trial of tridodecylmethyl-ammonium chloride pre-treated and M-R coated or untreated, uncoated catheters. This trial consisted of two hundred and eighty-one hospital patients who required venous catheterisation. The authors concluded that M-R coated catheters could significantly reduce both microbial colonisation and catheter-related bloodstream infection as no patients who received the M-R coated catheters developed an infection (Raad et al., 1997). This was further reinforced by a meta-analysis of antimicrobial catheters which concluded that minocycline-rifampin impregnated intravascular catheters were the most successful

at reducing the development of catheter-related bloodstream infection, especially when used for less than seven days.

A multiple subsequent meta-analysis by Falagas et al. (2007) and Casey et al. (2008b) compared control catheters with M-R impregnated central venous catheters found that they offered a reduced risk of microbial colonisation and catheter-related bloodstream infection. The use of rifampin-miconazole impregnated venous catheters was also found to offer a significant decrease in the risk of catheter-related bloodstream infections (Lorente et al., 2016). Alongside such antibiotic use in catheters, Hernández-Richter et al. (2003) demonstrated that rifampin incorporated vascular Dacron graft material provided a significant reduction in infection rate, when compared to a control. Rifampin containing products were even found to outperform silver or triclosan incorporated materials, following subcutaneous implantation and contamination with *S. aureus* (Hernández-Richter et al., 2003).

The potential to save an estimated $100 million through the use of such modified catheters has been suggested (Pai et al., 2001). Hanna et al. (2004) confirmed these finding with long-term study (100 days) of non-tunnelled silicone catheters impregnated with M-R in three hundred and sixty-five cancer patients. The results revealed that they were efficacious and safe in reducing catheter-related bloodstream infections in cancer patients, however it was acknowledged that there was an overall low infection rate across the trial (Hanna et al., 2004).

4.3.2. Gentamicin

As early as 1979, Olanoff et al. had incorporated gentamicin into the silicon rubber of a prosthetic heart valve to successfully reduce infection in dogs. More recently, the use of gentamicin loaded PDLLA coatings of indwelling devices has been examined. PDLLA is a biodegradable polymer which facilitates the release of gentamicin to protect the implant surface from microbial colonisation and infection. Lucke et al. (2003) showed the application of gentamicin loaded PDLLA coated titanium Kirschner wires to *S. aureus* contaminated rats significantly reduced the level of implant-related infection. This work was followed by examining gentamicin loaded PDLLA against a systematic delivery of gentamicin to reduce implant related osteomyelitis in a similar rat model. The authors concluded whilst systematic application of gentamicin reduced osteomyelitis in 15% of animals, local application through Kirschner wires coated in gentamicin loaded PDLLA, reduced bacterial infection by 90% (Lucke et al., 2005). Similarly, Vester et al. (2010) found that in a rat model a gentamicin loaded PDLLA coating of titanium implants successfully reduced bacterial adhesion to the implant site and therefore provided a suitable treatment to fight such infection. These results appear to suggest gentamicin loaded PDLLA could potentially help significantly reduce infection in human implantation.

Although gentamicin and Minocycline-rifampin incorporation appears to be a valuable option in reducing the microbial colonisation of indwelling medical devices, other antibiotics have been examined. Jansen et al. (1992) found that Hydrocath polyvinylpyrrolidone coated catheters whose surface was loaded with teicoplannin prevented *S. epidermidis* colonisation for 48 h *in vitro*. Similarly, lystostaphin coated polystyrene and FEP polymer catheters were shown to prevent surface colonisation and actively kill multiple strains of *S. aureus*. These catheters also seemed to retain full antimicrobial efficacy even when incubated with human serum which indicated that *in vivo* usage would not adversely affect their antimicrobial efficacy (Shah et al., 2004).

Teicoplanin-impregnated silicone knee cement spacers have been shown to be a highly effective method for eradicating already infected knee replacements. Twenty five patients were studied of which twenty four had been successfully treated with this technique (Buyuk et al., 2016). Tobramycin has also been prepared in bioresorbable microspheres, using a copolymerisation of 50% lactic and 50% glycolic acid which when used in rabbit model studies, revealed a significant level of infection prevention when implanted within metal orthopaedic implants infected with *S. aureus* (Ambrose et al., 2014).

5. Surface modification and intrinsic surface antibacterial strategies

Since the beginning of the twenty-first century there has been significant interest in the development of implants with chemically or topographically modified surfaces, or intrinsic contact-killing or repellent properties. Surfaces that actively disrupt and kill cells on contact are classified as antimicrobial. Antifouling materials which offer repellent properties are regarded as anti-biofouling. Bacterial surface attachment occurs though multiple mechanisms including hydrophobic and electrostatic interactions (Nagel et al., 1996). From a chemical and physicochemical modification perspective, antifouling surfaces usually focus on imposing three properties to repel microbial attachment; hydrophobicity, negative charge or low surface energy.

5.1. Charged surfaces

5.1.1. Heparin

Since the late 1980's modification of surfaces by means of heparin coatings have been shown to reduce bacterial adhesion by inducing increased surface hydrophilicity, causing a highly hydrated interface. Ruggieri et al. (1987), demonstrated when catheters of latex, Teflon coated latex and vinyl were ionically coated with a complex of heparin and tridodecylmethylammonium chloride (TDMAC), bacterial adhesion was significantly reduced. This was especially evident for latex catheters where bacterial adhesion was reduced to less than 10% compared with an untreated control. Further, a study by Riedl et al. (2002) suggested that a polyurethane ureteral stents and silicone nephrostomy tubes with a heparin coating effectively inhibited all biofilm formation over a six week period. It has been suggested that heparin-coated antibiotic impregnated catheters might be an effective approach to reduce catheter related bloodstream infections. Investigation into the synergistic co-impregnation of catheters with silver and heparin have also shown strong biocidal and anti-thrombogenic properties (Croes et al., 2011; Stevens et al., 2011).

5.1.2. Poly(ethylene glycol) (PEG)

Immobilised PEG based surface coatings are among the most studied hydrophilic antifouling coatings. It has been suggested that if a material can resist the surface adsorption of proteins, the adhesion of bacteria will be severely limited (Ostuni et al., 2001). However, in practice the addition of such protein inhibitors, for example PEG coatings, to a wide range of medical synthetic polymers has shown mixed results in its ability to reduce bacterial adhesion, be it in either the form of a steric barrier of polymer brushes or self-assembled monolayers (SAMs). Park et al. (1998b) demonstrated that PEG modified polyurethane with either a terminal hydroxyl, amino or sulfonate group showed mixed resistance to *S. epidermis* adhesion, and was dependant on the terminal group, molecular weight and growth media. Kingshott et al. (2003) also reported that PEG coated stainless steel could not reduce adhesion of *Pseudomonas* sp. when compared with a control. However, a poly (ethylene terephthalate) (PET)/PEG surface was able to reduce adhesion by up to 4 orders of magnitude for 5 h (Kingshott et al., 2003). A recent interpretation of results of the bactericidal efficacy of PEG SAMs led to suggestions by Banerjee et al. (2011) that a protein resistant surface did not necessarily equate to a bacterial resistant surface. In addition, another issue is the surface attachment of PEG and therefore potential surface protein absorption cannot be reduced below a threshold level since steric forces limit the attachment density (Banerjee et al., 2011). PEG also oxidises after long periods in complex media, thus further developments are needed to reduce bacterial adhesion on indwelling medical devices in the current form (Kane et al., 2003; Cheng et al., 2008).

5.1.3. Novel surface attached dendrimers and polymer brushes

Functional coatings using polymer brushes have been used to

covalently secure antimicrobial peptides (AMP's) to a surface. Paris et al. (2017) demonstrated the use of natural antiadhesive and biocidal products (hyaluronic acid and nisin) covalently bonded to polyethylene could reduce S. *epidermidis* adhesion by 99.8% *in vitro*. Similarly, Li et al. (2017) used a thiol-ol reaction to graft two natural antibacterial polymers (agarose (AG) and quaternized chitosan (QCS)) to a both polyvinyl fluoride and polyurethane with the aim of reduced biofilm formation. The AG coating achieved a > 2 log reduction against *P. aeruginosa* and *S. aureus* biofilm formation and the QSC reduced surface associated bacteria by > 95% (Li et al., 2017). Gao et al. (2016) grafted a compound, consisting of a dodecyl-alkylated quaternary ammonium and a benzophenone moiety, on to the surface of polyethylene (PE) and polyvinyl acetate (PVA) samples. Significant and rapid efficacy was noted against *S. aureus* and *E. coli* with the surface antimicrobial activity being restored simply by the removal of the dead bacteria (Gao et al., 2016). Although the above findings were positive, further *in vivo* testing must be conducted to fully explore the host environment interactions and biomolecular conditioning with the antimicrobial surfaces to fully establish the efficacy of such surfaces.

5.2. Biological and Naturally derived strategies

5.2.1. Antimicrobial peptides (AMPs)

Antimicrobial peptides are the innate defence molecules used by animals, plants and microorganisms, which have been used as a design template for large variety of synthetically produced AMPs. AMPs are most often amphipathic, cationic peptides that offer a broad spectrum of antimicrobial activity. It has been suggested that AMPs are unlikely to lead to developed resistance due to their distinctive mechanisms, in addition, they are highly biocompatible and can modulate the innate host immune response (Ragland and Criss, 2017; Chin et al., 2018). Furthermore, in recent years AMPs have displayed significant potential to treat infections caused by multidrug-resistant pathogens (Mohammad et al., 2015; Riool et al., 2017). Most studies examining the efficacy of AMPs have focused on titanium surfaces, for the use in orthopaedic medicine, and most *in vivo* testing has been performed on titanium surfaces (Li et al., 2015; Chen et al., 2016; Rai et al., 2016; Ye et al., 2016; Cheng et al., 2017; Nilebäck et al., 2017; Yu et al., 2017). A recent study by Yu et al. (2017) highlighted the potential for the integration of AMP strategies into polymeric medical implants. Yu et al. (2017) attached AMP E6 via brush coating tethering to a PU catheter and *P. aeruginosa, S. aureus* and *S. saprophyticus* were chosen to challenge the product in both *in vitro* and an *in vivo* mouse urinary infection model to examine bacterial adherence. The polymer brush and AMP E6 combination demonstrated a significant decrease in bacterial adherence (> 4 log reduction) against all species over the duration of the experiment. A previous study by Lim et al. (2015) had also shown the proof of concept regarding surface immobilisation of another potent synthetic antimicrobial peptide, CWR11, on pieces of a silicone coated Foley catheter via an initial Polydopamine (PD) pre-treatment. The authors concluded, by using SEM and confocal microscopy analysis, that the PD-CWR11 treatment significantly reduced the attachment and biofilm formation of *E. coli*, *S. aureus* and GFP-*P. aeruginosa* when compared with the untreated sample (Lim et al., 2015). Similarly, Li et al. (2014) conducted experiments using *E. coli*, *S. aureus* and *C. albicans* to challenge two novel AMPs, RK1 and RK2, tethered to the surface of silicon catheters by allyl glycidyl ether (AGE) polymer brushes. The results of *in vitro* testing in growth medium, showed significant reductions in biofilm formation on both RK1 and RK2 containing samples, when compared with a control (Li et al., 2014). Additionally, Dutta et al. (2016) highlighted the antimicrobial efficacy of four AMPs (*viz.* LL-37, melimine, lactoferricin and Mel-4) when immobilised on Polyhydroxymethacrylate (pHEMA), a common polymer used for medical applications. The results suggested that pHEMA with immobilised melamine and LL-37 showed the greatest inhibition of both *P. aeruginosa* and *S. aureus,* with melamine displaying the greatest efficacy against both organisms (Dutta et al., 2016). Nilebäck et al. (2017) recently demonstrated another method tethering AMPs by using biologically active peptides to functionalise a PU surface, amongst others. The authors used recombinant silk protein assemblies on the surfaces to form nanofibrillar structures and therefore impart an antimicrobial effect through the attachment of magainin, an antimicrobial peptide. Confocal microscopy showed that the combination of polystyrene, magainin and silk showed a significantly lower bacterial load than polystyrene or silk and just polystyrene, after 24h and 48h (Nilebäck et al., 2017). Finally, although surface attached peptides seemingly have a promising future in implant protection there are still some developments needed. For example, the antimicrobial activity can be severely affected by the tethering procedure (Dutta et al., 2016). Development is also needed to enable production of these surfaces in order to increase the transition from preliminary research to clinical trials and commercial products (Riool et al., 2017; Townsend et al., 2017).

5.2.2. Chitosan [poly-(b-1/4)-2-amino-2-deoxy-D-glucopyranose]

Chitosan is the collective name given to the range of antimicrobial polymers based on partially or fully deacetylated chitin. Whilst the exact mode of action is not yet fully understood, it is hypothesised that the positively charged chitosan interacts with the negatively charged bacterial cell membrane, leading to leakage of vital intracellular constituents. Chitosan has been demonstrated to possess antibacterial and antifungal properties against a wide range of microbial species (Muzzarelli et al., 1990; No et al., 2002; Rabea et al., 2003). The ability of surfaces coated with chitosan to resist biofilm formation of bacteria and yeast has also been documented (Carlson et al., 2016). Over a period of 54 h, synthetic polymers showed reductions in biofilm viability between 95% and 99.9%, when compared to a control against *S. epidermidis*, *S. aureus*, *K. pneumoniae*, *P. aeruginosa* and *C. albicans*. Most notably, under the same experimental conditions, the coatings containing chlorhexidine did not significantly reduce surface-associated growth, whereas the chitosan coatings recorded over a 99.9% reduction (Carlson et al., 2016). A pre-infected *in vivo* central venous catheter animal model to demonstrate that chitosan coated polyethylene catheters inhibited biofilm formation, whilst significantly reducing the microbial burden when compared with a control over 24 h (Rabea et al., 2003). Using a *in vivo* mouse model Corbrado et al. (2013) also reported the ability of polyurethane catheters coated at sub-inhibitory concentrations of chitosan to significantly reduce biofilm formation of *S. epidermidis* and *C. albicans,* which are two of the major causative species associated with catheter-related bloodstream infection.

5.2.3. Lactobacillus derived biosurfactants

The use of biosurfactants has also offered a potentially promising method of reducing the ability of bacteria to form biofilms on indwelling medical devices. For example, biosurfactants isolated from *Lactobacillus fermenti* and *Lactobacillus rhamnosus* were used to impregnate the surface layer of polystyrene samples and demonstrated a reduction in adhesion of *E. coli*, *K. pneumoniae* and *P. aeruginosa* (Brzozowski et al., 2011). Similarly, Velraeds et al. (1997) suggested the development of catheter material incorporating the biosurfactant, surlactin, which is produced by *Lactobacillus acidophilus.* However, the authors did conclude that these were only preliminary results and that the composition of suspension media and hydrophobicity of both substrata and suspension media, as well as, the specific pathogens involved may play a part in their observations (Velraeds et al., 1997).

6. The economics of polymeric implantation

The CDC has previously reported that approximately 250,000 central venous catheter (CVC) related bloodstream infection (BSI) cases occur each year in the USA alone, with the cost attributable to each infection being between ca. $34,500 – $56,000. This puts the annual

cost at dealing with CVC-associated BSI patients between $296 million and $2.3 billion (O'Grady et al., 2011). Similarly in the UK, CAUTIs were found to account for 65,000–74,000 patients annually and cost ca. £125 million pounds a year to treat (Buckley et al., 2017).

The estimated usage of medical polymers is set to keep rising with the 2017 USA market valued at ca. $5 billion and forecasted to rise to ca. $7 billion by 2020. This trend is also replicated globally with the 2016 global polymers market size estimated to be $20.5 billion and expect to rise to between ca. $33 billion by 2025 (Grand View Research, 2018). The global market size for only polymer based devices is also predicted to rise by 8% compound annual growth rate (CAGR) by 2024 (Global Market Insights, 2017; Grand View Research, 2017). Within this sector, polyether ether ketone (PEEK) and PE, especially ultra-high molecular weight polyethylene (UHMWPE) are often suggested by researchers and market forecasters to have the greatest market growth. This market attractiveness is mainly due to the inherent biocompatibility, structural strength, radiolucency, inert nature and commercial viability of these polymers providing an extensive potential for future developments across a large range of implant categories (Gunatillake and Adhikari, 2016; Singh and Chavan, 2016).

Catheters are the most common implant worldwide, with 5 million CVC's and 30 million urinary catheters being implanted per year, in the USA alone (Kornbau et al., 2015; Levering et al., 2016). With both catheters variants identified as two of leading origins of HAIs, the economic impacts of catheterisation can often be significant (Havard, 2014; Leeson and Webber, 2017). The calculations can be complicated by how to decide the overall cost of a BSI. Many suggestions have been proposed, the NHS cost perspective assumes 6 additional days for ICU patients or 5 for general ward patients (Hockenhull et al., 2008), whilst in the USA Goudie et al. (2014) found the extended stay could be up to 19 days (Goudie et al., 2014). This discrepancy highlights the problem of separating the increased hospitalisation due to BSI from the original condition, as patients who are more ill are more likely to acquire a BSI. Often quality-adjusted life years (QALYs) are used as an economic indicator, however this can be difficult to calculate for BSIs, due to increased risk of further infection and the problem of how to accurately determine the relevant timespan to calculate the incremental cost-effectiveness ratio (ICER). Hockenhull et al. (2008) also proposed the economic practicality of silver incorporated catheters. The results from use in the England and Wales National Health Services (NHS) showed a cost saving per patient receiving a C-SS coated catheter of approximately £138 in reduced total medical expense. In addition, randomised, blind clinical trials conducted separately by Ostendorf et al. (2005) and Brun-Buisson et al. (2004) found a similar reduction in microbial colonisation of catheters and a trend towards lowered infection rates in patients with a C-SS implant. Lorente et al. (2014) presented a favourable cost analysis of chlorhexidine-silver sulfadiazine-impregnated CVCs and suggested, at least in the USA, they would provide a cost and health benefit over standard CVCs. Ridyard et al. (2017) demonstrated that antibiotic (rifampicin and minocycline) impregnated CVCs reduced the occurrence of blood stream infection (BSI) in paediatric intensive care units (PICUs) in the UK. However, due to the low incidence rate of BSI in these locations and the increased cost of the antibiotic impregnated CVCs, which on average cost ca. £31–36 extra per unit, their general application might not currently provide an overall cost-effective scheme (Ridyard et al., 2017). Harron et al. (2016) used data from the same controlled trials as Ridyard et al. (2017) and concluded that antimicrobial impregnated central venous catheters (CVCs) did offer a reduced-cost alternative to managing the BSI associated with standard CVCs, even at the low level of incidence presented (Harron et al., 2016). Kilonzo et al. (2012) suggest that, while the use of nitrofurazone-impregnated catheters may offer value for money to the UK's NHS, silver alloy-coated catheters were very unlikely to provide a similar benefits. The authors also noted that, in this situation, the cost saving would have been modest at, on average, £7 less than a standard catheter over 6 weeks. Thus, it can be demonstrated that the financial advantages of using such modified systems are not straightforward and it is difficult to recommend which system might be the best to use.

7. Global standardisation - implant regulations

The development of the antimicrobial technology and consequential increase in patient wellbeing, is the ultimate goal of such antimicrobial surface development. A key barrier to market is the cost and time required to satisfy the individual regulatory standards of each economic region. A major point of discussion, is the large difference in regulatory frameworks between the USA and the EU (Sorenson and Drummond, 2014). Systematic post-market surveillance could be insightful to assess product safety, and real world capabilities, especially on specific subsets of patients and circumstances. Currently in the USA and until recently for the EU postmarket, reporting on implants was for the most part, voluntary (Kramer et al., 2012). There was also further concerns about the rigorousness of the EU regulatory body Conformité Européenne (CE) due to the increased level of safety alerts and product recalls being 13% compared to the USA (27%) (Hwang et al., 2016). Furthermore, many of the products recalled in the EU had never been granted approval in the USA (US Food and Drug Administration, 2012). In 2017, the EU updated their medical device regulations with the MDR 2017/745 directive. This directive aims to address the problems in post-market analysis by increasing the legal demand for device traceability and failure reporting.

8. The need for holistic systematic strategies

Long-term approaches using combination or synergistic strategies which provide active antimicrobial options could offer great potential for controlling implant associated infections. However, successful development of such antimicrobial systems requires a greater fundamental understanding of the phenotypic and genotypic characteristics of clinically relevant biofilms. This must be harmonised with additional extrinsic factors, such as improved biocompatibility. Furthermore, implant incorporated techniques must be used in conjunction with healthcare-wide strategies including preoperative procedures, surgical sterilisation and appropriate infection control procedures. A rigorous and practically tested anti-infection protocol must be developed, across the patient's entire hospital stay.

While the development of new and better anti-infection strategies is greatly needed, the proper use of developed strategies at all stages of a patients stay is paramount. Umscheid et al. (2011) identified this problem as they estimated 65%–70% of central line associated bloodstream infection (CLABSIs) and catheter associated urinary tract infections (CAUTIs) in the USA could be prevented with the proper implementation of current evidence-based strategies. The implementation of such systems has the potential to reduce infections and the subsequent costs of staffing and treatments involved, increase patient welfare, reduce patient morbidity and mortality and thus reduce overall infection associated costs. Landrigan et al. (2010) found complementary results in a retrospective patient review in which they estimated more than 75% of HAIs could have potentially been prevented, providing a potential national saving, if the trend was consistent across the USA, of ca. $5 billion a year.

Multiple clinicians have tried to address these problems by implementing the use of Corporate performance-improvement methodologies, such as Lean Six Sigma, which use data-driven quality-improvement methodology to standardise processes and reduce associated costs (Pyzdek and Keller, 2010). Frankel et al. (2005) first showed the benefit of the Six Sigma techniques on reducing CRBSIs, demonstrating a 650% reduction (from a CRBSI rate of 11 to 1.7 per 1000 catheter days) in infection rate. Loftus et al. (2015) also implemented the Six Sigma Define-Measure-Analyze-Improve-Control (DMAIC) model to successfully reduce CLABSIs in a neurotrauma intensive care unit. The authors also highlighted the need for a multidisciplinary approach, the

necessity for expert guidance and education at all levels. Such a collaborative effort may provide a system wide understanding of the standardised evidence-based protocol. Galiczewski and Shurpin (2017) showed that even just the act of having an experienced clinician observe the procedure, and ensure a standardised evidence-based check list for catheterisation, reduced the incidence of CAUTIs from 2.24 to 0 per 1000 catheter days. To make the most of these approaches, an organisation wide implementation is often stressed, but this would require long-term organisational policy and strategic planning initiatives (Deblois and Lepanto, 2016).

9. Conclusion

To provide a significant decrease in HAI prevalence all issues must be simultaneously addressed, and implemented. This includes further development and investigation into device incorporated antimicrobial technologies, refinement and rigorous adherence of aseptic technique along with continual education and training programmes for relevant healthcare professionals. The continued rise of global antibiotic resistance only increases the importance of efforts to reduce the instances of infection. The focus on strategies which prevent pathogenic biofilm formation may be the key to decreasing serious infection, especially as the complete eradication of microbes is unrealistic. The generation of post-market real-world evidence must also be utilised to provide a complete understanding of efficacy and cost-effectiveness in such environments.

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Appendix A. Supplementary data

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